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THE PATENTS ACT, 1952, AS AMENDED.

APPLICATION FOR A PATENT UNDER INTERNATIONAL ARRANGEMENTS
(WITH AUTHORISATION OF AGENT)

Filing date and Application No.

681802

& CO.

of Applicant(s): MERCK & CO., Inc.

Address(es) of applicant(s): 126 East Lincoln Avenue
Rahway, New Jersey
United States of America

Full name(s) of inventor(s):

MARCIA ELIZABETH CHRISTY

I/We do hereby declare that I am/we are in possession of an invention the title of which is

"5,10-METHANO DERIVATIVES OF 10,11-DIHYDRODIBENZOCYCLO-
HEPTENES AND PROCESSES"

I am/We are the assignee(s)/legal representative(s) of the inventor(s). Application(s) for protection for the invention has/have been made in the following country/countries and on the following official dates i.e.:—

- | | | | | | |
|--------------|--------------------------|--------|---------------|----------|---------|
| 1. (country) | United States of America | (date) | 21 March 1967 | (number) | 624,705 |
| 2. (country) | | (date) | | (number) | |
| 3. (country) | | (date) | | (number) | |

The said application or each of the said applications was the first application in a convention country in respect of the relevant invention by me/us or by any person from whom I/we derive title. To the best of my/our knowledge and belief there is no lawful ground for objection to the grant of a patent to me/us on this application. I/We pray that a patent be granted to me/us for the invention in priority over other applicants and that such patent shall have the official date of the first application in a convention country i.e. 21 March 1967.

I/We hereby appoint the partners and qualified staff of the firm of D. M. KISCH & Co., jointly and severally, to act for me/us in all matters relating to this application and any letters patent granted thereon.

Dated this 7th day of February 1968

Address for service:

D. M. KISCH & CO.,

CORPORATION BUILDING,
COMMISSIONER STREET,
JOHANNESBURG.

MERCK & CO., Inc.

Table of Classification	
Class	Sub-class

Stephen C. Zelenak
Stephen C. Zelenak
Administrative Assistant-Patents

Signature of Applicant/s and Capacity

REPUBLIC OF SOUTH AFRICA

THE PATENTS ACT, 1952, AS AMENDED

COMPLETE SPECIFICATION

Filing date and Application No.

68/1802



20-3-1968

Full name(s) of Applicant(s): MERCK & CO., INC.

Address(es) of Applicant(s): 126 East Lincoln Avenue, Rahway, New Jersey,
United States of America

Title of Invention: "5,10-METHANO DERIVATIVES OF 10,11-DIHYDRODIBENZOCYCLO-
HEPTENES AND PROCESSES"

I/We do hereby declare this invention, the manner in which and the method by which it is
to be performed, to be particularly described and ascertained in and by the following
statement:—

1 This invention relates to 10,11-dihydro-5,10-
2 methano derivatives of dibenzocycloheptenes having the 5-
3 position substituted by an organic radical and, particularly,
4 the invention relates to 10,11-dihydro-5,10-methanodibenzo-
5 cycloheptenes having a saturated or unsaturated alkyl sub-
6 stituent or a saturated or unsaturated substituted-alkyl
7 substituent attached to the 5-position.

8 The invention includes 10,11-dihydro-5,10-methano-
9 dibenzocycloheptenes having a 5-position aminoalkyl side
10 chain optionally further substituted by ketonic oxygen,
11 hydroxyl and, in addition, is saturated or unsaturated.

12 The invention also includes 5-alkanoyl-10,11-di-
13 hydro-5H-dibenzo[a,d]cycloheptene compounds which are inter-
14 mediates in the preparation of the biologically-active
15 compounds of my invention.

16 The invention also relates to methods of preparing
17 5-aminoalkyl-10,11-dihydro-5,10-methanodibenzocycloheptene
18 compounds and to intermediates in the preparation of said
19 compounds from 9-alkanoyl, e.g., 9-acetylanthracycline compounds
20 such as 9-alkanoyl-9,10-dihydro-9,10-ethano-11-(carboxy or
21 carbalkoxy)anthracene compounds, 5-alkanoyl-10,11-dihydro-
22 5,10-methano-11-(acyloxy or hydroxy)dibenzocycloheptene
23 compounds.

24 The new compounds representative of my invention
25 are 5,10-methano-10,11-dihydrodibenzocycloheptene compounds
26 which contain alkyl, alkanoyl or alkanoyloxy substituents at
27 the 5-position of the dibenzocycloheptene molecule. Repre-
28 sentative groups of compounds included within the scope of
29 my invention are those in which the 5-alkyl substituent is
30 substituted at any of the carbon atoms of the side chain

1 with a primary amine, a secondary amine, or a tertiary amine
2 substituent, particularly, N-alkylated secondary or tertiary
3 amine groups wherein the N-alkyl radicals are methyl, ethyl,
4 propyl, isopropyl, butyl, secondary butyl, isobutyl and
5 t-butyl substituents.

6 There are also included tertiary aminoalkyl-
7 substituted compounds in which the tertiary amine nitrogen is
8 linked in a heterocyclic ring containing 5 or 6 members which
9 optionally contains additional hetero atoms such as nitrogen,
10 oxygen or sulphur linked with the requisite number of carbons
11 to complete the 5- or 6-membered heterocyclic ring.

12 Also included within the scope of my invention are
13 compounds which contain additional functional substituents
14 attached to any of the carbons of the alkyl side chain.
15 These substituents include hydroxyl, ketonic oxygen, acyloxy,
16 (particularly alkanoyloxy), halo and/or amino (primary,
17 secondary or tertiary amino including heterocyclic amino of
18 the type mentioned hereinabove).

19 The compounds of my invention include 5-alkyl or
20 substituted-alkyl 5,10-methano-10,11-dihydrodibenzocyclo-
21 heptene compounds wherein the 5-alkyl or substituted-alkyl
22 radicals include both saturated and unsaturated derivatives
23 including 5-methyl, ethyl, propyl, isopropyl, butyl, branched-
24 chain butyl such as isobutyl, secondary butyl and t-butyl as
25 well as pentyl and hexyl, and the corresponding unsaturated
26 derivatives such as 5-vinyl, propenyl, isopropenyl, butenyl,
27 pentenyl and hexenyl 5,10-methano-10,11-dihydrodibenzocyclo-
28 heptenes, especially including those compounds wherein the
29 double bond of the unsaturated side chain at the 5-position
30 is attached to the carbon linking the unsaturated side chain

1 to the dibenzocycloheptene nucleus, e.g., 5-(1-propenyl)-
2 5,10-methano-10,11-dihydrodibenzocycloheptene.

3 Especially preferred compounds of my invention
4 are 5-substituted 5,10-methano-10,11-dihydrodibenzocyclo-
5 heptene compounds wherein the substituent attached to the
6 5-position is an aminoalkyl substituent, an alkylaminoalkyl
7 substituent, a dialkylaminoalkyl substituent or a hetero-
8 cyclicaminoalkyl substituent. Such compounds include
9 5-(aminoalkyl)-5,10-methano-10,11-dihydrodibenzocycloheptene,
10 5-(N-alkylaminoalkyl)-5,10-methano-10,11-dihydrodibenzocyclo-
11 heptene, 5-(N,N-dialkylaminoalkyl)-5,10-methano-10,11-dihydro-
12 dibenzocycloheptene, and 5-(heterocyclicaminoalkyl)-5,10-
13 methano-10,11-dihydrodibenzocycloheptene. The alkyl side
14 chain through which the aminoalkylamino or heterocyclic amino
15 substituent is linked to the dibenzocycloheptene nucleus at
16 the 5-position is optionally a straight or branched-chain
17 alkyl substituent, preferably of from 1 to 6 carbon atoms as,
18 for example, methyl, ethyl, propyl, isopropyl, butyl or
19 branched-chain butyl, pentyl or hexyl or branched-chain
20 pentyl or hexyl radicals.

21 In addition to the above-mentioned 5,10-methano-
22 dibenzocycloheptene compounds, the intermediate 9,10-ethano-
23 9,10-dihydroanthracene compounds form part of my invention.
24 These intermediate compounds are prepared by heating a
25 9-alkanoylanthracene compound with acrylic acid or a function-
26 ally equivalent derivative thereof such as an acrylic acid
27 ester, acrylonitrile, or the like, to produce the desired
28 9-alkanoyl-9,10-ethano-9,10-dihydroanthracene-11-carboxylic
29 acid (alkyl carboxylate or nitrile).

30 The new compounds of my invention, including the

1 intermediate compounds as well as the pharmaceutically-
 2 active end products, also include substituents at the 11-
 3 position. The substituents are selected from the group con-
 4 sisting of H, OH, OY, =NOR^o, =NOY, NH₂, NHSO₂R, N_{R'''}^{R°} =NNH₂
 5 and, in the case wherein the substituent is OH or OY, there
 6 can be an alkyl group as defined by R''' replacing the hydrogen
 7 at the 11-position; wherein R is lower alkyl, straight or
 8 branched-chain, preferably having up to 6 carbon atoms,
 9 $-(CH_2)_n-\text{[cyclohexyl]}-(B)_n$ wherein B is hydrogen, halogen, tri-
 10 fluoromethyl, lower alkyl, straight or branched-chain,
 11 preferably having up to 4 carbon atoms, lower alkoxy, straight
 12 or branched-chain, preferably having up to 4 carbon atoms,
 13 and n represents a whole number of from 0 to 3; R° is
 14 hydrogen or lower alkyl, straight or branched chain, prefer-
 15 ably having up to 6 carbon atoms, R''' is lower alkyl, straight
 16 or branched chain, preferably having up to 6 carbon atoms;
 17 Y is alkanoyl, straight or branched-chain, preferably having
 18 up to 18 carbon atoms and may contain unsaturation,
 19 $-\overset{O}{\underset{||}{C}}-(CH_2)_n-\text{[cyclohexyl]}-(B)_n$ wherein B and n are as defined
 20 above.

21 Representative compounds encompassed within the
 22 scope of the present invention include:
 23 10,11-dihydro-5,10-methano-11-hydroxy-5-[3-(1-piperidyl)-
 24 propyl]-5H-dibenzo[a,d]cycloheptene,
 25 10,11-dihydro-5,10-methano-11-hydroxy-5-[3-(1-methyl-4-
 26 piperazinyl)-propyl]-5H-dibenzo[a,d]cycloheptene.
 27 10,11-dihydro-5,10-methano-11-hydroxy-5-(3-dimethylaminopropyl)-
 28 5H-dibenzo[a,d]cycloheptene,
 29 10,11-dihydro-5,10-methano-11-hydroxy-5-(3-methylaminopropyl)-
 30 5H-dibenzo[a,d]cycloheptene,
 31 7-chloro-10,11-dihydro-5,10-methano-11-hydroxy-5-(3-dimethyl-
 32 aminopropyl)-5H-dibenzo[a,d]cycloheptene,

- 1 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-methano-11-
- 2 hydroxyimino-3-methylsulfonyl-5H-dibenzo[a,d]cycloheptene,
- 3 11-methylamino-10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-
- 4 methano-5H-dibenzo[a,d]cycloheptene,
- 5 11-diethylamino-10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-
- 6 methano-5H-dibenzo[a,d]cycloheptene,
- 7 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-methano-11-ethyl-
- 8 11-hydroxy-5H-dibenzo[a,d]cycloheptene,
- 9 10,11-dihydro-5,10-methano-11-hydroxy-5-(3-methylaminopropyl)-
- 10 3-methylsulfonyl-5H-dibenzo[a,d]cycloheptene,
- 11 10,11-dihydro-5,10-methano-11-hydroxy-5-(3-dimethylamino-
- 12 propyl)-3-trifluoromethyl-5H-dibenzo[a,d]cycloheptene,
- 13 10,11-dihydro-5,10-methano-11-hydroxy-5-(3-diethylamino-
- 14 propyl)-3-dimethylsulfamoyl-5H-dibenzo[a,d]cycloheptene,
- 15 10,11-dihydro-5,10-methano-5-(3-dimethylaminopropyl)-5H-
- 16 dibenzo[a,d]cycloheptene,
- 17 10,11-dihydro-5,10-methano-5-(3-methylaminopropyl)-5H-dibenzo-
- 18 [a,d]cycloheptene,
- 19 10,11-dihydro-5,10-methano-5-(3-methylaminopropyl)-3-methyl-
- 20 sulfonyl-5H-dibenzo[a,d]cycloheptene,
- 21 10,11-dihydro-5,10-methano-5-(3-dimethylaminopropyl)-3-tri-
- 22 fluoromethyl-5H-dibenzo[a,d]cycloheptene,
- 23 10,11-dihydro-5,10-methano-5-(3-diethylaminopropyl)-3-dimethyl-
- 24 sulfamoyl-5H-dibenzo[a,d]cycloheptene,
- 25 11-acetoxy-10,11-dihydro-5,10-methano-5-(3-methylaminopropyl)-
- 26 3-trifluoromethyl-5H-dibenzo[a,d]cycloheptene,
- 27 11-benzoyloxy-10,11-dihydro-5,10-methano-5-(3-methylamino-
- 28 propyl)-5H-dibenzo[a,d]cycloheptene,
- 29 11-p-chlorobenzoyloxy-10,11-dihydro-5-(3-dimethylaminopropyl)-
- 30 5,10-methano-5H-dibenzo[a,d]cycloheptene,
- 31 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-methano-11-p-
- 32 tosyloxy-5H-dibenzo[a,d]cycloheptene,
- 33 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-methano-11-p-
- 34 methoxybenzoyloxy-5H-dibenzo[a,d]cycloheptene,
- 35 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-methano-11-m-
- 36 trifluoromethylbenzoyloxy-5H-dibenzo[a,d]cycloheptene,
- 37 10,11-dihydro-5,10-methano-5-(3-methylaminopropyl)-11-phenyl-
- 38 acetoxy-5H-dibenzo[a,d]cycloheptene,
- 39 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-methano-11-
- 40 hydrocinnamoyloxy-5H-dibenzo[a,d]cycloheptene,

- 1 10,11-dihydro-5,10-methano-5-(3-methylaminopropyl)-11-
- 2 propionyloxy-5H-dibenzo [a,d] cycloheptene,
- 3 11-acetoxylimino-10,11-dihydro-5-(3-dimethylaminopropyl)-3-
- 4 dimethylsulfamoyl-5,10-methano-5H-dibenzo [a,d] cycloheptene,
- 5 11-benzoyloxyimino-10,11-dihydro-5,10-methano-5-(3-methyl-
- 6 aminopropyl)-5H-dibenzo [a,d] cycloheptene,
- 7 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-methano-11-
- 8 phenylacetoxylimino-5H-dibenzo [a,d] cycloheptene,
- 9 11-p-chlorobenzoyloxyimino-10,11-dihydro-5-(3-dimethyl-
- 10 aminopropyl)-5,10-methano-5H-dibenzo [a,d] cycloheptene,
- 11 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-methano-11-p-
- 12 tosyloxyimino-5H-dibenzo [a,d] cycloheptene,
- 13 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-methano-11-
- 14 phenylacetoxylimino-5H-dibenzo [a,d] cycloheptene,
- 15 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-methano-11-
- 16 hydrocinnamoyloxyimino-5H-dibenzo [a,d] cycloheptene,
- 17 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-methano-11-
- 18 propoxyimino-5H-dibenzo [a,d] cycloheptene,
- 19 11-benzenesulfonamido-10,11-dihydro-5-(3-dimethylaminopropyl)-
- 20 5,10-methano-5H-dibenzo [a,d] cycloheptene,
- 21 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-methano-11-p-
- 22 toluenesulfonamido-5H-dibenzo [a,d] cycloheptene,
- 23 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-methano-11-
- 24 phenylmethanesulfonamido-5H-dibenzo [a,d] cycloheptene,
- 25 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-methano-5H-
- 26 dibenzo [a,d] cycloheptene-N-oxide,
- 27 10,11-dihydro-11-dimethylamino-5,10-methano-5-(3-dimethyl-
- 28 aminopropyl)-5H-dibenzo [a,d] cycloheptene-N,N'-dioxide,
- 29 2-methoxy-10,11-dihydro-5,10-methano-11-hydroxy-5-(3-dimethyl-
- 30 aminopropyl)-5H-dibenzo [a,d] cycloheptene,
- 31 4-ethoxy-7-trifluoromethyl-10,11-dihydro-5,10-methano-11-hydroxy-
- 32 5-(3-dimethylaminopropyl)-5H-dibenzo [a,d] cycloheptene,
- 33 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-methano-11-
- 34 hydroxyimino-2-methoxy-5H-dibenzo [a,d] cycloheptene,
- 35 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-methano-11-hydroxy-
- 36 imino-4-ethoxy-7-trifluoromethyl-5H-dibenzo [a,d] cycloheptene,
- 37 10,11-dihydro-5,10-methano-11-hydroxy-5-(3-methylaminopropyl)-
- 38 2-methoxy-5H-dibenzo [a,d] cycloheptene,
- 39 10,11-dihydro-5,10-methano-11-hydroxy-5-(3-methylaminopropyl)-
- 40 4-ethoxy-7-trifluoromethyl-5H-dibenzo [a,d] cycloheptene,

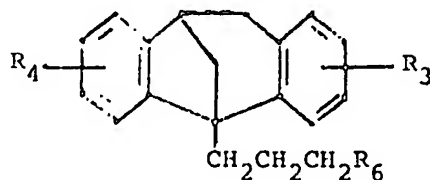
1 10,11-dihydro-5,10-methano-11-hydroxy-5-(3-dimethylamino-
 2 propyl)-2-methoxy-5H-dibenzo[a,d]cycloheptene,
 3 10,11-dihydro-5,10-methano-11-hydroxy-5-(3-dimethylamino-
 4 propyl)-4-ethoxy-7-trifluoromethyl-5H-dibenzo[a,d]cyclo-
 5 heptene,
 6 10,11-dihydro-5,10-methano-11-hydroxy-5-(3-diethylaminopropyl)-
 7 2-methoxy-5H-dibenzo[a,d]cycloheptene,
 8 10,11-dihydro-5,10-methano-11-hydroxy-5-(3-diethylaminopropyl)-
 9 4-ethoxy-7-trifluoromethyl-5H-dibenzo[a,d]cycloheptene,
 10 10,11-dihydro-5,10-methano-5-(3-methylaminopropyl)-2-methoxy-
 11 5H-dibenzo[a,d]cycloheptene,
 12 10,11-dihydro-5,10-methano-5-(3-methylaminopropyl)-4-ethoxy-
 13 7-trifluoromethyl-5H-dibenzo[a,d]cycloheptene,
 14 10,11-dihydro-5,10-methano-5-(3-dimethylaminopropyl)-2-methoxy-
 15 5H-dibenzo[a,d]cycloheptene,
 16 10,11-dihydro-5,10-methano-5-(3-dimethylaminopropyl)-4-ethoxy-
 17 7-trifluoromethyl-5H-dibenzo[a,d]cycloheptene,
 18 10,11-dihydro-5,10-methano-5-(3-diethylaminopropyl)-2-methoxy-
 19 5H-dibenzo[a,d]cycloheptene,
 20 10,11-dihydro-5,10-methano-5-(3-diethylaminopropyl)-4-ethoxy-
 21 7-trifluoromethyl-5H-dibenzo[a,d]cycloheptene,
 22 11-acetoxy-10,11-dihydro-5,10-methano-5-(3-methylaminopropyl)-
 23 2-methoxy-5H-dibenzo[a,d]cycloheptene,
 24 11-acetoxy-10,11-dihydro-5,10-methano-5-(3-methylaminopropyl)-
 25 4-ethoxy-7-trifluoromethyl-5H-dibenzo[a,d]cycloheptene,
 26 11-benzoyloxy-10,11-dihydro-5,10-methano-2-methoxy-5-(3-methyl-
 27 aminopropyl)-5H-dibenzo[a,d]cycloheptene,
 28 11-benzoyloxy-10,11-dihydro-5,10-methano-4-ethoxy-7-trifluoro-
 29 methyl-5-(3-methylaminopropyl)-5H-dibenzo[a,d]cycloheptene.

30 The new compounds of my invention possess valuable
 31 pharmacological properties which may be exhibited by tests
 32 on animals. Thus, these new compounds of my invention have an
 33 action on the central nervous system of the intact animal
 34 which reverses the effect of certain depressants. Such com-
 35 pounds are useful in pharmaceutical applications as anti-
 36 depressants.

37 In addition, the new compounds can be used as
 38 starting materials or as intermediate products in the

1 manufacture of other valuable compounds. For example, the
2 amines form water-insoluble salts with penicillin G and
3 thus can be utilized in the precipitation and recovery of
4 penicillin G or other valuable organic acids.

5 The compounds which are especially useful are
6 compounds which are represented by the general formula:



7 in which:

8 R_3 and R_4 represent an alkyl, an alkoxy, a halo, a trifluoro-
9 methyl, an alkylsulfonyl or an alkylsulfamoyl sub-
10 stituent; and in which

11 R_6 represents an amino or an aminoalkyl substituent.

12 In these preferred compounds of my invention, the
13 R_6 substituent may be a free amino group, but it is preferably
14 a monoalkylamino, i.e., methylamino, ethylamino, propylamino,
15 isopropylamino or butylamino, or a dialkylamino substituent
16 such as diethylamino, dimethylamino, dipropylamino, dibutyl-
17 amino, or diisopropylamino. In addition, the amino substituent
18 may form a heterocyclic ring having, together with carbon,
19 nitrogen or oxygen, from about 5 to 6 atoms in the rings,
20 including such heterocyclic radicals as N-loweralkyl-
21 pyrrolidinyl, 1-pyrrolidyl, N-loweralkylpiperidinyl,
22 N-loweralkylpiperidylidene-4-morpholinyl and 1-loweralkyl-4-
23 piperizinyl. Especially effective compounds representative
24 of the active compounds of my invention are 1-(10,11-dihydro-
25 5,10-methano-5H-dibenzo[a,d]cycloheptene-5-yl)-3-dimethyl-
26 amino-1-propanol; 1-(10,11-dihydro-5,10-methano-5H-dibenzo-
27 [a,d]cycloheptene-5-yl)-3-dimethylamino-1-propanone;

5-(3-dimethylamino-1-propenyl)-10,11-dihydro-5,10-methano-5H-dibenzo[a,d]cycloheptene and 5-(3-dimethylaminopropyl)-10,11-dihydro-5,10-methano-5H-dibenzo[a,d]cycloheptene.

The processes for preparing the compounds of the present invention are illustrated in the flowsheet wherein X is carboxy or esterified carboxy such as COO-loweralkyl, R₁₁ is hydroxyl or alkanoyloxy, R₁ is alkyl or substituted alkyl including aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, or heterocyclicaminoalkyl in which the heterocyclic substituent is attached to the aliphatic side chain through the aminonitrogen atom which is included in a cycle of atoms of carbon, nitrogen or oxygen to form a ring of 5 or 6 atoms, including 1-piperidyl, 1-pyrrolidyl, 4-morpholinyl and 1-loweralkyl-4-piperiziny1 and R₃ and R₄ are as defined previously.

In accordance with my invention, a 9-alkanoyl anthracene is heated with an unsaturated lower aliphatic acid such as acrylic acid or an ester thereof (Compound I hereinabove) to form the corresponding 9-alkanoyl-9,10-ethano-11-carboxy or carbalkoxydihydroanthracene (II), and subsequently converting said carboxy or carbalkoxy compound into the corresponding 11-carboxylic acid hydrazide by reaction, for example, of the 11-carboxylic acid ester with hydrazine to form the corresponding 11-carboxylic acid hydrazide, reacting said hydrazide with nitrous acid and hydrolyzing the resulting urethane under acidic conditions to the desired 9-alkanoyl-11-amino-9,10-ethano-9,10-dihydroanthracene (Compound III hereinabove).

The resulting 9-alkanoyl-11-amino-9,10-ethano-9,10-dihydroanthracene is then heated in intimate contact

1 heterocyclicaminoalkyl in which the heterocyclic substituent is
2 attached to the aliphatic side chain through the aminonitrogen
3 atom which is included in a cycle of atoms of carbon, nitrogen
4 or oxygen to form a ring of 5 or 6 atoms, including 1-piperidyl,
5 1-pyrrolidyl, 4-morpholinyl and 1-loweralkyl-4-piperizinyl,
6 and in which the dotted line at the 5-position indicates that
7 the compound may be saturated or unsaturated at the indicated
8 side chain position (C_1 , C_2).

9 In accordance with my invention, a 9-alkanoyl
10 anthracene is heated with an unsaturated lower aliphatic
11 acid such as acrylic acid or an ester thereof (Compound I
12 hereinabove) to form the corresponding 9-alkanoyl-9,10-
13 ethano-11-carboxy or carbalkoxydihydroanthracene, and subse-
14 quently converting said carboxy or carbalkoxy compound into
15 the corresponding 11-carboxylic acid hydrazide by reaction,
16 for example, of the 11-carboxylic acid ester with hydrazine
17 to form the corresponding 11-carboxylic acid hydrazide,
18 reacting said hydrazide with nitrous acid and hydrolyzing
19 the resulting urethane under acidic conditions to the
20 desired 9-alkanoyl-11-amino-9,10-ethano-9,10-dihydroanthra-
21 cene (Compound III hereinabove).

22 The resulting 9-alkanoyl-11-amino-9,10-ethano-
23 9,10-dihydroanthracene is then heated in intimate contact
24 with nitrous acid and an organic acid to form a 5-alkanoyl-
25 10,11-dihydro-5,10-methano-11-hydroxy or acyloxy-5H-dibenzo-
26 [a,d]cycloheptene (Compound IV hereinabove).

27 Compound IV is then heated under acidic conditions
28 in the presence of an amine and an aldehyde, particularly
29 formaldehyde, to introduce an aminoalkyl, preferably a
30 dialkylaminomethyl substituent, into the alkanoyl side chain

in a lower alkanol to remove the chloro substituent and produce Compound XIII. Compound XIII is then heated under acidic conditions in the presence of an amine and an aldehyde to introduce an aminoalkyl substituent into the alkanoyl side chain and form the desired compound XIV which is reduced to Compound VIII by heating in the presence of an alkali metal borohydride.

The formed aminoalkanol VIII is then dehydrated by heating in the presence of an acidic dehydrating agent such as phosphorus oxychloride, whereby a double bond is introduced into the 5-position side chain of the compound and there is formed a 5-alkylaminoalkenyl-5,10-methano-10,11-dihydro-5H-dibenzo[a,d]cycloheptene IX. This compound IX is then catalytically hydrogenated to saturate the side chain double bond with resultant formation of a 5-alkyl-aminoalkyl-5,10-methano-10,11-dihydro-5H-dibenzo[a,d]cycloheptene X.

Thus, the process of my invention involves the conversion of a 9-alkanoylanthracene compound to produce a 5,10-methano-10,11-dihydro-5H-dibenzo[a,d]cycloheptene containing an alkylaminoalkyl substituent attached to the 5-position.

It is, of course, clear that many variations of the above-mentioned process may be employed but, as such, they are presumed to be included within the scope of my invention. Thus, my process involves the addition

1 of an unsaturated compound across the 9,10-position of
2 the 9-alkanoylanthracene starting material, rearrangement
3 of the resulting 9,10-ethano-9,10-dihydroanthracene under
4 acidic conditions to produce the desired 5,10-methano-
5 10,11-dihydro-5H-dibenzo[a,d]cycloheptene nucleus, and
6 elaboration of the alkanoyl side chain at the 5-position
7 of said 5,10-methano compound to produce a 5,10-methano-
8 10,11-dihydro-5H-dibenzo[a,d]cycloheptene having an alkyl-
9 aminoalkyl side chain at the 5-position. The details of
10 this process are set forth hereinbelow.

11 In converting 9-alkanoylanthracene, e.g., 9-acetyl-
12 9-propionoyl-9-butyryl-9-valeryl or 9-hexanoylanthracene to
13 the corresponding 9-alkanoyl-9,10-ethano-11-carboxy or carb-
14 alkoxy dihydroanthracene, the starting material is heated
15 with acrylic acid or a derivative thereof as, for example,
16 a loweralkyl ester, to produce the corresponding 9-alkanoyl-
17 11-carboxy or carbalkoxy-9,10-ethanodihydroanthracene. In
18 carrying out the reaction, it is preferable to heat a mixture
19 of the reactants at the reflux temperature for a period of
20 from a few minutes to 24 hours and, preferably, for a period
21 of about 1 to 3 hours.

22 The reaction may be conducted in the presence of
23 an inert high boiling solvent either as a liquid aromatic
24 compound including phenol ethers, halogenated or nitro-
25 substituted benzene, such as anisole, o-dichlorobenzene,
26 nitrobenzene, and the like. However, it is preferred in
27 the present instance to carry out the reaction by heating a
28 mixture of the alkanoylanthracene and the acrylic acid or
29 derivative thereof together for the recommended period of
30 time using excess acrylic acid derivative as solvent medium.

1 Acrylic acid derivatives which may be used as reactants in
2 this addition reaction include methyl, ethyl, propyl, iso-
3 propyl, butyl, amyl and hexyl esters of acrylic acid. The
4 product obtained in the case of the 11-carboxylic acid
5 derivative is readily separated from the reaction mixture
6 by dissolving in aqueous alkali and precipitation from acid,
7 followed by recrystallization from mixtures of lower alkanols
8 and water.

9 In carrying out the reaction with lower alkyl
10 ester of acrylic acid, it is preferred to conduct the reaction
11 in a dry, inert solvent in the presence of a small amount of
12 an acidic catalyst such as the halide of aluminum, and heat
13 the entire reaction mixture for a period of from about 2 to
14 50 hours and, preferably, for a period of from about 15 to
15 30 hours. Following reaction, the entire mixture is diluted
16 with an aqueous acid and the solvent layer containing the
17 formed product is separated, washed and dried. The product
18 is obtained by crystallization from a concentrated solution.

19 The formed 9-alkanoyl-11-carboxy or carbalkoxy
20 9,10-ethanodihydroanthracene (Compound II hereinabove) is
21 then converted to the corresponding 9-alkanoyl-11-amino-
22 9,10-ethano-9,10-dihydroanthracene by, first, conversion
23 to the acid azide and degradation to the amino compound.
24 This is conveniently accomplished either by reaction of
25 the free acid with hydrazoic acid, whereby the 11-amino
26 compound is formed directly or by first converting the
27 loweralkyl ester by reaction with hydrazine to the corres-
28 ponding hydrazide. Reaction of the thus-formed hydrazide
29 with nitrous acid results in production of the intermediate
30 11-urethane which is readily hydrolyzed under acidic

1 conditions to the corresponding 11-amino-9,10-ethanodi-
2 hydroanthracene.

3 In carrying out the conversion of the 11-carboxy
4 or 11-carbalkoxy-9-alkanoyl-9,10-dihydroanthracene to the
5 corresponding 11-amino compound, it is preferred to first
6 protect the 9-alkanoyl side chain as, for example, by
7 formation of a ketal of the side chain substituent. This
8 may be conveniently done by reaction of the 9-alkanoyl-11-
9 carboxy or carbalkoxy-9,10-ethanoanthracene with a lower-
10 alkanol or a 1,2 or 1,3 loweralkylene glycol, such as
11 ethylene glycol, 1,3 propylene glycol, or butane-diol
12 (1,2 or 1,3) in the presence of an acid.

13 In the preferred instance, the 11-carboxy-9-
14 alkanoyl-9,10-ethanodihydroanthracene or the corresponding
15 ester thereof is heated in the presence of ethylene glycol
16 admixed with a catalytic amount of an acid such as p-toluene-
17 sulfonic acid, to form the corresponding dioxolane of the
18 side chain carbonyl substituent.

19 Conversion of the thus-formed alkyl-9,10-dihydro-
20 9-(1-alkylenedioxyalkyl)-9,10-ethano-11-carboxy compound to
21 the corresponding 11-carboxy ester is carried out in the
22 same manner as previously described for the corresponding
23 9-alkanoyl-9,10-ethano-11-carboxy-9,10-dihydroanthracene
24 compounds. The resulting esterified dioxolane derivative
25 is then reacted with hydrazine to form the corresponding
26 carboxylic acid hydrazide. The formed hydrazide is then
27 heated with nitrous acid to form the 11-amino derivative.
28 When the dioxolane derivative is used, rearrangement of the

1 11-carboxylic acid hydrazide to the 11-amino compound
2 results in simultaneous hydrolysis of the dioxolane moiety
3 and regeneration of the 9-alkanoyl side chain.

4 The resulting 9-alkanoyl-11-amino-9,10-ethano-
5 dihydroanthracene is then heated with nitrous acid to form
6 5-alkanoyl-5,10-methano-11-hydroxy-5H-dibenzo[a,d]cyclo-
7 heptene (Compound IV hereinabove).

8 When the reaction is carried out in a solvent
9 which is unreactive with the formed product, the compound
10 is readily isolated by evaporation of the solvent and
11 separation of the product in crude form. In the event that
12 the reaction is carried out in a loweralkanoic acid, the
13 product obtained is the 11-acyloxy compound corresponding
14 thereto wherein the 11-hydroxyl substituent is esterified by
15 reaction with the reacting solvent alkanoic acid. In a
16 preferred instance of the reaction, a 9-alkanoyl-11-amino-
17 9,10-ethano-9,10-dihydroanthracene is heated in contact with
18 nitrous acid in a solution of glacial acetic acid to form
19 a mixture of products comprising principally the 11-acetoxy
20 derivative of 5-alkanoyl-5,10-methano-5H-dibenzo[a,d]cyclo-
21 heptene, along with a small amount of the corresponding
22 11-hydroxy derivative.

23 The resulting product, i.e., the 11-acyloxy or
24 the 11-hydroxy compound (Compound IV hereinabove) is then
25 heated under acidic conditions in the presence of an amine
26 and an aldehyde in order to elaborate the side chain alkanoyl
27 substituent and form a 5-dialkylaminoalkanoyl-5,10-methano-
28 10,11-dihydro-5H-dibenzo[a,d]cycloheptene. This reaction is
29 preferably carried out by reaction of formaldehyde and a
30 secondary amine such as a dialkylamine or a heterocyclic

1 amine wherein the amino nitrogen is included in the 5 or 6-
2 membered heterocyclic ring comprising carbon, nitrogen and/or
3 oxygen and sulfur, preferably a diloweralkylamine, with
4 Compound IV hereinabove either present as the 11-acyloxy,
5 the 11-hydroxy, or the corresponding compound containing
6 only hydrogen as a substituent at the 11-position. The
7 compound which is formed (indicated as Compound V herein-
8 above) is the corresponding 5-dialkylaminoalkanoyl-5,10-meth-
9 ano-5H-dibenzo[a,d]cycloheptene having an acyloxy, a hydroxy,
10 or hydrogen substituent at the 11-position.

11 The reaction is preferably carried out by mixing
12 the dialkylamine as the acid salt as, for example, a hydro-
13 chloride, with paraformaldehyde and an inert organic solvent,
14 hydrocarbon solvents being preferred such as benzene, nitro-
15 benzene, and the like. The entire reaction mixture is heated
16 to from 50°C. to the reflux temperature of the reaction
17 mixture for a period of from a few minutes to 24 hours,
18 preferably for a period of time of about 15 minutes to 1
19 hour. Higher temperatures may be employed but they are
20 impractical since the reaction goes essentially to completion
21 in a short time at the reflux temperature of the mixture.

22 Following the reaction, during which the desired
23 dialkylaminoalkanoyl-5,10-methanodibenzocycloheptene is
24 formed, the water formed during the reaction is distilled as
25 an azeotrope and the product precipitates as the acid salt
26 which may be recovered by filtration. The resulting alkyl-
27 aminoalkanoyl compound is then reduced by reaction with an
28 alkali metal borohydride such as potassium or sodium boro-
29 hydride, to the corresponding dialkylaminoalkanol-
30 substituted compound (Compound VI hereinabove).

1 In the event the dialkylaminoalkanoyl compound
2 submitted to this reduction procedure contains an acyloxy
3 substituent at the 11-position in accordance with one of
4 the preferred embodiments of my invention the acyloxy sub-
5 stituent is hydrolyzed during the course of the reduction
6 reaction and the formed product is recovered as the
7 11-hydroxy derivative thereof. Thus, reaction of the corres-
8 ponding 1-(10,11-dihydro-5,10-methano-11-acetoxy-5H-dibenzo-
9 [a,d]cyclohepten-5-yl)-3-dimethylamino-1-propanone results
10 in formation of 1-(10,11-dihydro-5,10-methano-11-hydroxy-
11 5H-dibenzo[a,d]cyclohepten-5-yl)-3-dimethylamino-1-propanol.

12 Similarly, reaction of 1-(10,11-dihydro-5,10-
13 methano-5H-dibenzo[a,d]cyclohepten-5-yl)-3-dimethylamino-
14 1-propanone with potassium borohydride results in the pro-
15 duction of the corresponding 3-dimethylamino-1-propanol
16 compound.

17 The reaction may be carried out from 0°C. to
18 100°C., although it is preferably carried out at from 15 to
19 30°C. under aqueous conditions. The starting 1-propanone
20 compound, being only partly soluble in water, is dissolved
21 in a loweralkanol as, for example, methanol, ethanol,
22 propanol, and the like, and is mixed with a solution of the
23 alkali metal borohydride, e.g., sodium or potassium boro-
24 hydride in water made slightly alkaline with sodium hydroxide.

25 The product of the reduction reaction is convenient-
26 ly recovered as the acid salt thereof by removal of the solvent
27 by distillation under reduced pressure and extraction of the
28 residual reaction mixture with benzene. The acid salt as,
29 for example, the fumarate, is then purified by recrystalliza-
30 tion from a solution of a loweralkanol, e.g., ethanol. The

1 product obtained in this manner may then be dehydrated
2 by heating in the presence of an acidic dehydrating agent
3 as, for example, phosphorus oxychloride and phosphorus
4 pentoxide, and the like. The aminoalkanol (Compound VI
5 hereinabove) in solution in benzene or chloroform or other
6 inert solvents, is mixed with an excess amount of phosphorus
7 oxychloride and heated to the reflux temperature of the
8 solvent for a period of from 1 to 30 hours at reflux
9 temperature.

10 The product obtained as a result of the dehydra-
11 tion reaction is the desired 5-dialkylaminoalkenyl-5,10-
12 methano-5H-dibenzo[a,d]cycloheptene (Compound VII herein-
13 above) mixed with the corresponding 5(1-chloro-3-dialkylamino)
14 compound wherein the dotted line of the formula represents
15 a double bond in the indicated position of the side chain.
16 The unsaturated product and (or the halo-substituted product)
17 obtained in this manner is then catalytically reduced to
18 saturate the side chain and produce the corresponding 5-
19 alkylaminoalkyl-5,10-methano-10,11-dihydro-5H-dibenzo[a,d]
20 cycloheptene.

21 The compounds of my invention can advantageously
22 be employed in pharmaceutical applications because they
23 have been found to possess antidepressant activity. As
24 antidepressants, they may be administered orally in the form
25 of tablets, powders, sustained release pellets and the like
26 or they may be administered orally or parenterally in the
27 form of aqueous solutions or suspensions. When administered
28 orally or parenterally, satisfactory results are obtained
29 at a daily dosage level of from about 1 mg. to about 300 mgs.
30 preferably given in divided doses over the day or in sus-
31 tained release form. The compounds are preferably

1 administered in the form of their non-toxic acid addition
2 salts and these salts are included within the scope of this
3 invention. In addition, the 5,10-methanodibenzocycloheptene
4 compounds represented by Formulas VI and VII may be converted
5 to the N oxides. These compounds, as well as their acid
6 addition salts, possess antidepressant activity and are
7 also included within the scope of my invention.

8 The following examples are presented to illustrate
9 the methods of carrying out the present invention.

10 Example 1

11 9-Acetyl-9,10-dihydro-9,10-ethanoanthracene-11-carboxylic
12 acid

13 A solution of 9-acetylanthracene (11.6 g., 0.0525
14 mole) in 30 ml. of acrylic acid (stabilized with p-methoxy-
15 phenol) is heated to refluxing for 2-1/2 hours. The cooled,
16 viscous mixture is dissolved in 20% aqueous sodium hydroxide
17 while cooling in an ice bath. The resulting solution is
18 added to an excess of ice-cold 6 N. hydrochloric acid and
19 the gummy precipitate collected, washed with water, and
20 crystallized from a mixture of ethanol and water with
21 decolorization with decolorizing carbon. The white crystal-
22 line 9-acetyl-9,10-dihydro-9,10-ethanoanthracene-11-carboxy-
23 lic acid, m.p. 169-171°C dec., when recrystallized from
24 ethanol-water, gives product, m.p. 172-174°C. dec. A
25 purified sample melts at 172.5-174.5°C. dec.

26 Anal. calc'd. for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52.
27 Found: C, 77.94; H, 5.50.

28 Example 2

29 9,10-Dihydro-9-(2-methyl-1,3-dioxolan-2-yl)-9,10-ethano-
30 anthracene-11-carboxylic acid

31 9-Acetyl-9,10-dihydro-9,10-ethanoanthracene-11-

1 carboxylic acid (2.5 g., 0.00855 mole), p-toluene sulfonic
2 acid monohydrate (100 mg.), ethylene glycol (8 ml.) and
3 dry toluene (75 ml.) are mixed and heated to refluxing
4 under a Dean-Stark water separator for 12 hours. Solvent
5 is evaporated under reduced pressure. The residual oil
6 containing the product is dissolved in 10 ml. of 95%
7 ethanol and heated to refluxing with 10 ml. of 10% aqueous
8 sodium hydroxide for 1-1/2 hours. Ethanol is distilled
9 under reduced pressure and the residual alkaline solution
10 diluted with water and added to an excess of ice-cold 6 N
11 hydrochloric acid. The precipitate is collected, washed
12 with water, and crystallized from 50% ethanol, m.p. 239-246°C.
13 A purified sample melts at 250-252°C. after repeated re-
14 crystallizations from 50% alcohol.

15 Anal. calc'd. for $C_{21}H_{20}O_4$: C, 74.99; H, 5.99.
16 Found: C, 74.62; H, 5.99.

17 Example 3

18 Methyl-9,10-dihydro-9-(2-methyl-1,3-dioxolan-2-yl)-9,10-
19 ethanoanthracene-11-carboxylate

20 A dry ethereal solution (50 ml.) containing
21 about 1.4 g. (0.033 mole) of diazomethane is added to a
22 stirred suspension of 9,10-dihydro-9-(2-methyl-1,3-
23 dioxolan-2-yl)-9,10-ethanoanthracene-11-carboxylic acid
24 (1.95 g., 0.0058 mole) in 50 ml. of absolute ether cooled
25 in an ice bath. The ice bath then is removed and the
26 mixture stirred at room temperature overnight. Solvent is
27 evaporated at room temperature and under reduced pressure
28 and the residue dissolved in absolute ether. After
29 filtration from a small amount of insoluble material, the

1 solution is evaporated and the residual colorless glass
2 containing the product crystallized from a mixture of
3 ethanol and water, m.p. 128-131°C. Repeated recrystal-
4 lizations from 60% ethanol give a purified product,
5 m.p. 128-130°C.

6 Anal. calc'd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33.
7 Found: C, 75.39, H, 6.23.

8 Example 4

9 Methyl-9-acetyl-9,10-dihydro-9,10-ethanoanthracene-11-
10 carboxylate

11 A solution of 9-acetyl-9,10-dihydro-9,10-
12 ethanoanthracene-11-carboxylic acid (2.92 g., 0.01 mole)
13 and p-toluenesulfonic acid monohydrate (100 mg.) in 60 ml.
14 of absolute methanol is heated to refluxing for 3-1/2 hours.
15 Solvent is evaporated under reduced pressure and the residual
16 oil dissolved in benzene (30 ml.). After washing with 5%
17 aqueous sodium hydroxide and water and drying by filtration
18 through anhydrous magnesium sulfate, the benzene is evapo-
19 rated under reduced pressure. The residue consists of the
20 crystalline product, m.p. 90-94°C. A purified sample melts
21 at 95-97°C., after repeated recrystallizations from ether-
22 petroleum ether.

23 Anal. calc'd. for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92.
24 Found: C, 78.93; H, 5.81.

25 Example 5

26 Methyl-9-acetyl-9,10-dihydro-9,10-ethanoanthracene-11-
27 carboxylate

28 A solution of methyl acrylate (34.4 g., 0.4 mole,
29 freshly redistilled under nitrogen, b.p. 78.5 - 79.5°C.) in
30 40 ml. of dry benzene is added dropwise over a 10 minute
31 period to a stirred suspension of anhydrous aluminum

1 chloride (5.33 g., 0.04 mole) in 150 ml. of dry benzene
 2 warmed to about 50°C. The clear solution is stirred and
 3 maintained at about 50°C. while a solution of 9-acetyl-
 4 anthracene (44. g., 0.2 mole) in 50 ml. of dry benzene is
 5 added. The mixture is stirred and heated in a slow stream
 6 of nitrogen at 60-65°C. for 21 hours. After cooling the
 7 mixture in an ice-bath, 100 ml. of 6 N. hydrochloric acid
 8 is added. The benzene layer is separated, re-extracted
 9 with 100 ml. 6 N. hydrochloric acid, washed with three
 10 100 ml. portions of water, and dried over anhydrous sodium
 11 sulfate. Evaporation of the benzene under reduced pressure
 12 and crystallization of the oily residue from a mixture of
 13 hexane and benzene affords the product, m.p. 101-103°C.
 14 This product gives no depression in melting point on ad-
 15 mixture with an authentic sample of methyl-9-acetyl-9,10-
 16 dihydro-9,10-ethanoanthracene-11-carboxylate prepared by
 17 the procedure described in Example 4.

18 Example 6

19 Methyl-9,10-dihydro-9-(2-methyl-1,3-dioxolan-2-yl)-9,10-
 20 ethanoanthracene-11-carboxylate

21 Methyl-9-acetyl-9,10-dihydro-9,10-ethanoanthra-
 22 cene-11-carboxylate (46 g., 0.15 mole), p-toluenesulfonic
 23 acid monohydrate (500 mg.), ethylene glycol (46 ml.) and
 24 dry benzene (550 ml.) are mixed and heated to refluxing
 25 under a Dean-Stark water separator for 8 hours. The mixture
 26 is transferred to a separatory funnel, the lower ethylene
 27 glycol phase removed, and the benzene phase washed with
 28 several 50 ml. portions of water. After drying by filtration
 29 through anhydrous sodium sulfate, the benzene is evaporated
 30 under reduced pressure and the residual oil comprising the

1 product crystallized from 30 ml. of 95% ethanol, m.p.
 2 127-130°. Recrystallization from 95% ethanol gives product
 3 with m.p. 128.5-130.5°.

4 Example 7

5 9,10-Dihydro-9-(2-methyl-1,3-dioxolan-2-yl)-9,10-ethano-
 6 anthracene-11-carboxylic acid hydrazide

7 Methyl-9-acetyl-9,10-dihydro-9-(2-methyl-1,3-
 8 dioxolan-2-yl)-9,10-ethanoanthracene-11-carboxylate (1.5 g.,
 9 0.0043 mole) is suspended in 7 ml. of hydrazine hydrate
 10 and the mixture is heated to refluxing for 15 minutes.
 11 Sufficient ethanol (5 ml.) is added to dissolve the suspended
 12 oil and the solution is heated to refluxing for 3 hours.
 13 During this period, white crystals separate and after cooling,
 14 the precipitate is collected and washed with 50% ethanol,
 15 m.p. 253-254°C. Repeated recrystallizations from absolute
 16 ethanol give an analytical sample, m.p. 254-255°C.
 17 Anal. calc'd. for $C_{21}H_{22}N_2O_3$: C, 72.26; H, 6.06,
 18 N, 8.03. Found: C, 71.97; H, 6.27, N, 8.04.

19 Example 8

20 9,10-Dihydro-11-ethoxycarbonylamino-9-(2-methyl-1,3-dioxolan-
 21 2-yl)-9,10-ethanoanthracene

22 A suspension of 9,10-dihydro-9-(2-methyl-1,3-
 23 dioxolan-2-yl)-9,10-ethanoanthracene-11-carboxylic acid
 24 hydrazide (4.8 g., 0.0138 mole) in 100 ml. of acetone is
 25 stirred and cooled to 0°C. in an ice-salt bath. The solid is
 26 dissolved by the addition of 9 ml. of 6 N. hydrochloric acid.
 27 A solution of sodium nitrite (965 mg., 0.014 mole) in 6 ml.
 28 of water is added dropwise and stirring at -5° to 0°C. is
 29 continued for 30 minutes. After the addition of 100 ml. of
 30 absolute ethanol and a 15 minute period of stirring at 0°C.
 31 the mixture is filtered. The filtrate is stirred with

7 oxychloride and heated to the reflux temperature of the
8 solvent for a period of from 1 to 30 hours at reflux
9 temperature.

10 The product obtained as a result of the dehydra-
11 tion reaction is the desired 5-dialkylaminoalkenyl-5,10-
12 methano-5H-dibenzo[a,d]cycloheptene (Compound VII herein-
13 above) mixed with the corresponding 5(1-chloro-3-dialkylamino)
14 compound wherein the dotted line of the formula represents
15 a double bond in the indicated position of the side chain.
16 The unsaturated product and (or the halo-substituted product)
17 obtained in this manner is then catalytically reduced to
18 saturate the side chain and produce the corresponding 5-
19 alkylaminoalkyl-5,10-methano-10,11-dihydro-5H-dibenzo[a,d]
20 cycloheptene.

21 The compounds of my invention can advantageously
22 be employed in pharmaceutical applications because they
23 have been found to possess antidepressant activity. As
24 antidepressants, they may be administered orally in the form
25 of tablets, powders, sustained release pellets and the like
26 or they may be administered orally or parenterally in the
27 form of aqueous solutions or suspensions. When administered
28 orally or parenterally, satisfactory results are obtained
29 at a daily dosage level of from about 1 mg. to about 300 mgs.
30 preferably given in divided doses over the day or in sus-
31 tained release form. The compounds are preferably

Example 10

11-Acetoxy-5-acetyl-10,11-dihydro-5,10-methano-5H-dibenzo-
[a,d]cycloheptene and 5-acetyl-10,11-dihydro-5,10-methano-
5H-dibenzo[a,d]cyclohepten-11-ol
9-Acetyl-11-amino-9,10-dihydro-9,10-ethano-
anthracene hydrochloride (4.2 g.; 0.014 mole) is suspended
in 40 ml. of glacial acetic acid and stirred while sodium
nitrite (3.9 g., 0.056 mole) is added in portions over
10-15 minutes. The temperature rises spontaneously to about
42°C. and gas evolution is vigorous. After stirring for
22 hours at room temperature, the reaction mixture containing
the product is filtered, washing the precipitate with glacial
acetic acid. Distillation of the acetic acid from the filtrate
under reduced pressure leaves a viscous oil containing a
mixture of 11-acetoxy-5-acetyl-10,11-dihydro-5,10-methano-
5H-dibenzo[a,d]cycloheptene and 5-acetyl-10,11-dihydro-5,10-
methano-5H-dibenzo[a,d]cyclohepten-11-ol that solidifies on
trituration with cold methanol. The precipitate is collected
and recrystallized from methanol, m.p. 141-144°C. Repeated
recrystallization of the product from methanol gives 11-ace-
toxy-5-acetyl-10,11-dihydro-5,10-methano-5H-dibenzo[a,d]-
cycloheptene melting at 142-144°C.

Anal. calc'd. for $C_{20}H_{16}O_3$: C, 78.41; H, 5.92.

Found: C, 78.48; H, 6.00.

The methanol filtrate from the precipitation of
11-acetoxy-5-acetyl-10,11-dihydro-5,10-methano-5H-dibenzo-
[a,d]cycloheptene is evaporated. The residual oily solid
is freed from oil by pressing out on a porous plate yielding 5-
acetyl-10,11-dihydro-5,10-methano-5H-dibenzo[a,d]cyclohepten-11-
ol), m.p. 136-163°C. A typical sample melts at 178.5-179.5°C.

1 after successive recrystallizations from ethanol-water,
2 isopropyl alcohol-water and absolute ether.

3 Anal. calc'd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10.

4 Found: C, 81.82; H, 6.09.

5 Example 11

6 5-Acetyl-10,11-dihydro-5,10-methano-5H-dibenzo[a,d]cyclo-
7 hepten-11-ol

8 11-Acetoxy-5-acetyl-10,11-dihydro-5,10-methano-
9 5H-dibenzo[a,d]cycloheptene (1.8 g.) is dissolved in 30 ml.
10 of 5% potassium hydroxide in 95% ethanol and the solution
11 is heated to refluxing for 1-1/2 hours. Evaporation of the
12 ethanol under reduced pressure and trituration of the residue
13 with water gives the solid product which is collected, dried,
14 and recrystallized from ether to obtain substantially pure
15 product, m.p. 167-177°. Recrystallization from ether
16 gives product, m.p. 174-177°.

17 Example 12

18 1-(11-Acetoxy-10,11-dihydro-5,10-methano-5H-dibenzo[a,d]-
19 cyclohepten-5-yl)-3-dimethylamino-1-propanone hydrochloride

20 A mixture of dimethylamine hydrochloride (165 mg.,
21 0.00202 mole), paraformaldehyde (70 mg., 0.00233 mole) and
22 concentrated hydrochloric acid (1 drop) is stirred and heated
23 to refluxing in 1 ml. of nitrobenzene and 1 ml. of benzene
24 for 20 minutes. During this period, the solids first form
25 a ball and then a colorless, lower second phase. 11-Acetoxy-
26 5-acetyl-5,10-methano-5H-dibenzo[a,d]cycloheptene (610 mg.,
27 0.002 mole) is added and the mixture is stirred at reflux
28 for 2 hours. During the last 5 minutes of this period, the
29 condenser is removed so that water in the mixture may distill
30 azeotropically. After cooling to room temperature and

1 filtration from a small quantity of precipitate, the filtrate
 2 is diluted with ether. The product precipitates and is
 3 collected, washed with ether, dried, and crystallized from
 4 isopropyl alcohol-ether, m.p. 181-183°C. dec. Repeated
 5 recrystallizations from isopropyl alcohol-ether give a
 6 purified product, m.p. 186-187°C. dec.

7 Anal. calc'd for $C_{23}H_{25}NO_3 \cdot HCl$: C, 69.07; H, 6.55;
 8 N, 3.50. Found: C, 68.85; H, 6.71; N, 3.37.

9 Example 13

10 1-(10,11-Dihydro-11-hydroxy-5,10-methano-5H-dibenzo[a,d]-
 11 cyclohepten-5-yl)-3-dimethylamino-1-propanol

12 1-(11-Acetoxy-10,11-dihydro-5,10-methano-5H-
 13 dibenzo[a,d]cyclohepten-5-yl)-3-dimethylamino-1-propanone is
 14 prepared from 4.22 g. (0.0105 mole) of the hydrochloride salt
 15 by rendering an aqueous solution of the salt strongly alkaline
 16 with 5% sodium hydroxide and extracting the oily base into
 17 benzene. Evaporation of the washed and dried benzene extract
 18 under reduced pressure leaves the oily residue which is
 19 dissolved in 250 ml. of methanol. A solution of potassium
 20 borohydride (1.13 g., 0.021 mole) in 6 ml. of water containing
 21 2 drops of 10 N. sodium hydroxide is added. After stirring
 22 for 6 hours and standing for 2 days at room temperature,
 23 methanol is distilled under reduced pressure. The residue is
 24 partitioned between benzene and water and the benzene extract
 25 is separated, washed, dried, and evaporated to dryness under
 26 reduced pressure. The product remains as the residual glass
 27 in quantitative yield. The base is converted to the hydrogen
 28 oxalate salt by treating an ethanolic solution with an
 29 equimolar amount of oxalic acid dissolved in ethanol. The
 30 1-(10,11-dihydro-11-hydroxy-5,10-methano-5H-dibenzo[a,d]-

1 cyclohepten-5-yl)-3-dimethylamino-1-propanol hydrogen oxalate
 2 precipitates, m.p. 195-197°C. A purified sample melts at
 3 199-200°C. after repeated recrystallizations from mixtures
 4 of absolute ethanol and methanol.

5 Anal. calc'd for $C_{21}H_{25}NO_2 \cdot C_2H_2O_4$: C, 66.81,
 6 H, 6.58, N, 3.39. Found: C, 66.55; H, 6.52; N, 3.51.

7 Example 14

8 1-(11-Chloro-10,11-dihydro-5,10-methano-5H-dibenzo[a,d]cyclo-
 9 hepten-5-yl)-3-dimethylamino-1-propanol hydrochloride

10 1-(10,11-Dihydro-11-hydroxy-5,10-methano-5H-
 11 dibenzo[a,d]cyclohepten-5-yl)-3-dimethylamino-1-propanol
 12 (0.75 g.; 0.00232 mole) is added in portions to 2.5 ml. of
 13 thionyl chloride with stirring and cooling in an ice bath.
 14 After 3-1/2 hours of stirring at room temperature, the excess
 15 thionyl chloride is distilled under reduced pressure and at
 16 room temperature. The residual glass is dissolved in absolute
 17 ethanol and the solution evaporated under reduced pressure.
 18 Addition and removal of ethanol is repeated and, finally,
 19 the residue is triturated with 3 ml. of acetone. The white
 20 crystalline hydrochloride of the product is collected, washed
 21 with ether and dried in vacuo, m.p. 182-190°C. dec. A
 22 purified sample melts at 192-194°C. dec. after recrystalli-
 23 zation from acetone.

24 Anal. calc'd for $C_{21}H_{24}ClNO \cdot HCl$: C, 66.68, H, 6.66,
 25 Cl, 18.74. Found: C, 66.64; H, 6.65; Cl, 18.66.

26 Example 15

27 1-(10,11-Dihydro-5,10-methano-5H-dibenzo[a,d]cyclohepten-5-yl)-
 28 3-dimethylamino-1-propanol

29 A dry, nitrogen-flushed flask is charged with
 30 1-(11-chloro-10,11-dihydro-5,10-methano-5H-dibenzo[a,d]-

1 mixture evaporated under reduced pressure. Crystallization
 2 of the residue from 95% ethanol affords the product, m.p.
 3 125-130°C. A purified sample melts at 128.5-130.5°C
 4 after repeated recrystallizations from 95% ethanol.

5 Anal. calc'd. for $C_{18}H_{15}ClO$: C, 76.45; H, 5.35;
 6 Cl, 12.54. Found: C, 76.23; H, 5.44; Cl, 12.52.

7 Example 18

8 5-Acetyl-10,11-dihydro-5,10-methano-5H-dibenzo[a,d]cyclo-
 9 heptene

10 A solution of 5-acetyl-11-chloro-10,11-dihydro-
 11 5,10-methano-5H-dibenzo[ad]cycloheptene (0.84 g., 0.00308
 12 mole) in 0.5 ml. triethylamine - 35 ml. absolute ethanol
 13 is hydrogenated at room temperature and atmospheric pressure
 14 in the presence of 70 mg. of 5% palladium on charcoal. When
 15 one equivalent of hydrogen is taken up, the reduction stops
 16 and catalyst is removed by filtration and washed with
 17 absolute ethanol. The filtrate is evaporated under reduced
 18 pressure and the residue triturated with absolute ether. The
 19 precipitate of triethylamine hydrochloride is removed by
 20 filtration, the filtrate evaporated and the residual solid
 21 crystallized from 95% ethanol, m.p. 105-107°C. A purified
 22 sample melts at 106-107°C. after recrystallization from 70%
 23 ethanol and sublimation at 80° and 0.05 mm.

24 Anal. calc'd. for $C_{18}H_{16}O$: C, 87.06; H, 6.50.
 25 Found: C, 87.00; H, 6.38.

26 Example 19

27 1-(10,11-Dihydro-5,10-methano-5H-dibenzo[a,d]cyclohepten-5-yl)-
 28 3-dimethylamino-1-propanone

29 A mixture of dimethylamine hydrochloride (265 mg.,
 30 0.00324 mole) paraformaldehyde (112 mg., 0.00372 mole) and

1 cyclohepten-5-yl)-3-dimethylamino-1-propanol hydrochloride
 2 (0.855 g., 0.00225 mole), tert-butyl alcohol (3.35 g.,
 3 0.045 mole) and 20 ml. of dry tetrahydrofuran. Under a slow
 4 stream of nitrogen, the suspension is stirred vigorously
 5 and freshly-cut small pieces of sodium (1.35 g.; 0.0575 g.
 6 atom) are added. The mixture is stirred and heated to reflux-
 7 ing for 6 hours. Excess sodium is destroyed by the slow
 8 addition of 10 ml. of absolute methanol. After cooling,
 9 the mixture is poured into 250 ml. of ice water and the
 10 oily base is extracted into 1:1 benzene-ether. Solvents are
 11 distilled from the washed and dried organic extract under
 12 reduced pressure, leaving the oily product as the residue.

13 The base (0.6 g., 0.00196 mole) is converted to
 14 the fumarate salt by treating an ethanolic solution with an
 15 equimolar amount of fumaric acid dissolved in ethanol. The
 16 1-(10,11-dihydro-5,10-methano-5H-dibenzo[a,d]cyclohepten-
 17 5-yl)-3-dimethylamino-1-propanol fumarate precipitates, m.p.
 18 231-233°C. dec. An analytical sample melts at 232-233°C.
 19 dec. after recrystallization from absolute ethanol.

20 Anal. calc'd. for $C_{23}H_{27}NO_3 \cdot 1/2 C_4H_4O_4$: C, 75.59;
 21 H, 7.45; N, 3.83. Found: C, 75.28; H, 7.38; N, 3.76.

22 Example 16

23 1-(10,11-Dihydro-5,10-methano-5H-dibenzo[a,d]cyclohepten-5-yl)-
 24 3-dimethylamino-1-propanol

25 With a stream of nitrogen passing through the
 26 solution, 55% hydriodic acid, 0.2 ml., is heated on the
 27 steam bath and decolorized by the addition of 1 drop of 50%
 28 hypophosphorous acid. Red phosphorus (25 mg., 0.0008 g.
 29 atom), 1-(10,11-dihydro-11-hydroxy-5,10-methano-5H-dibenzo-
 30 [a,d]cyclohepten-5-yl)-3-dimethylamino-1-propanol (66 mg.;

1 0.000204 mole), and 1 ml. of glacial acetic acid are added.
2 The mixture is stirred at reflux for 4 hours. Phosphorus
3 is removed by filtration and washed with glacial acetic acid.
4 The ice-cold filtrate is rendered strongly alkaline and the
5 oily base that separates is extracted into benzene. Evapo-
6 ration of the washed and dried benzene extract under
7 reduced pressure leaves an oil. This residue is heated to
8 refluxing for 1-1/2 hours in 1 ml. of 5% potassium hydroxide
9 in 95% ethanol. The solvent is evaporated under reduced
10 pressure and the residue partitioned between ether and water.
11 The ethereal layer is separated, washed with water, dried
12 by filtration through anhydrous magnesium sulfate, and
13 evaporated under reduced pressure. The residual oily base,
14 44 mg. (70%), is identical in infrared and proton magnetic
15 resonance spectra to the compound prepared according to the
16 previous example. Upon treatment with fumaric acid, the
17 product is converted to the fumarate salt, m.p. 231-232°C.
18 dec., that gives no depression in melting point on admixture
19 with the fumarate of the compound prepared according to the
20 previous example.

21 Example 17

22 5-Acetyl-11-chloro-10,11-dihydro-5,10-methano-5H-dibenzo-
23 [a,d]cycloheptene

24 5-Acetyl-10,11-dihydro-5,10-methano-5H-dibenzo-
25 [a,d]cyclohepten-11-ol (1.32 g., 0.005 mole) is added in
26 portions to 5 ml. of thionyl chloride with stirring and
27 cooling in an ice bath. After 4-1/2 hours of stirring at
28 room temperature, the excess thionyl chloride is distilled
29 under reduced pressure and at room temperature. The
30 residual solid is suspended in absolute ethanol and the

1 concentrated hydrochloric acid (2 drops) is stirred and
2 heated to refluxing in 1.6 ml. of nitrobenzene and 1.6 ml.
3 of benzene for 20 minutes. During this period, the solids
4 first form a ball and then a colorless, lower second phase.
5 5-Acetyl-10,11-dihydro-5,10-methano-5H-dibenzo[a,d]cyclo-
6 heptene (797 mg., 0.0032 mole) is added and the mixture is
7 stirred at reflux for 2-1/2 hours. During the final 15
8 minutes of this period, the condenser is removed so that
9 water in the mixture may distill azeotropically. On cooling,
10 the hydrochloride of the product precipitates and is collect-
11 ed, washed with ether, and triturated with boiling isopropyl
12 alcohol, m.p. 210-212°C. Recrystallization from mixtures
13 of absolute ethanol and absolute ether affords an analytical
14 sample, m.p. 211-213°C.

15 Anal. calc'd. for $C_{21}H_{23}NO \cdot HCl$: C, 73.77; H, 7.07;
16 N, 4.10. Found: C, 73.57; H, 6.94, N, 4.03.

17 Example 20

18 1-(10,11-Dihydro-5,10-methano-5H-dibenzo[a,d]cyclohepten-5-yl)-
19 3-dimethylamino-1-propanol

20 1-(10,11-Dihydro-5,10-methano-5H-dibenzo[a,d]-
21 cyclohepten-5-yl)-3-dimethylamino-1-propanone (376 mg.,
22 0.00123 mole) is dissolved in 15 ml. of absolute methanol.
23 A solution of potassium borohydride (135 mg., 0.0025 mole)
24 in 1 ml. of water containing 1 drop of 5% aqueous sodium
25 hydroxide is added and the mixture, after stirring at room
26 temperature for 3 hours, is maintained at 0 - 5°C. for 2 days.
27 Methanol is distilled under reduced pressure and the residue
28 partitioned between benzene and water. Evaporation of the
29 washed and dried benzene extract leaves the oily product
30 in a yield of 317 mg. The base is converted to the fumarate

2 amount of fumaric acid dissolved in ethanol. 1-(10,11-
3 dihydro-5,10-methano-5H-dibenzo[a,d]cycloheptene-5-yl)-3-
4 dimethylamino-1-propanol fumarate crystallizes, m.p. 228-230°C.
5 and gives no depression in melting point on admixture with
6 the product prepared according to the previous example.

7

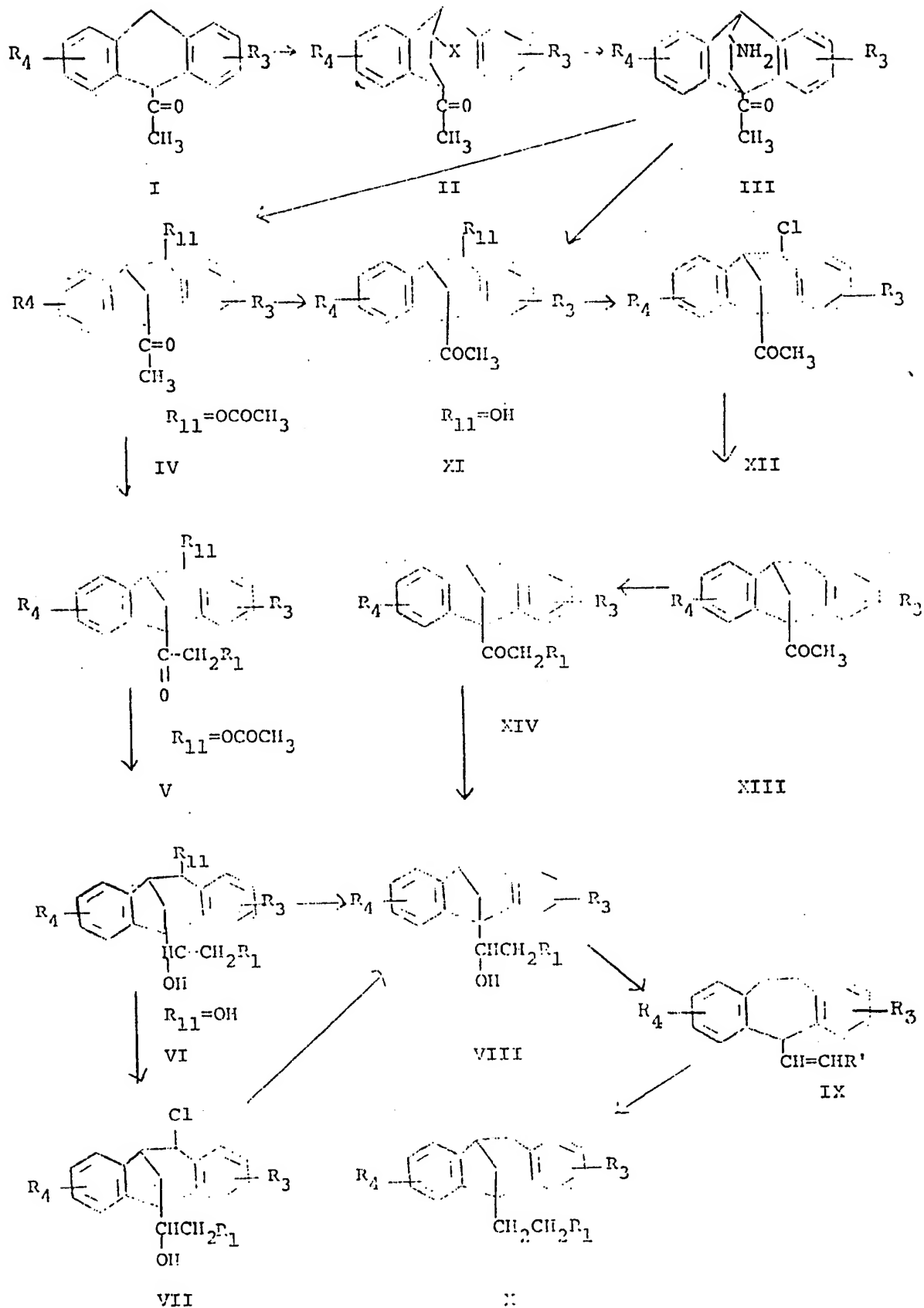
Example 21

8 10,11-Dihydro-5-(1-chloro-3-dimethylaminopropyl)-5,10-methano-
9 5H-dibenzo[a,d]cycloheptene and 1-(10,11-dihydro-5,10-methano-
10 5H-dibenzo[a,d]cycloheptene-5-yl)-3-dimethylamino-1-propene
11 1-(10,11-Dihydro-5,10-methano-5H-dibenzo[a,d]cyclo-
12 hepten-5-yl)-3-dimethylamino-1-propanol, 399 mg. (0.0013 mole),
13 is converted to the hydrochloride salt by treatment of a
14 benzene solution with an excess amount of ethanolic hydrogen
15 chloride. Evaporation of the solution under reduced pressure
16 leaves the white solid hydrochloride which is dried in vacuo
17 at 70°C. A suspension of the hydrochloride in 2 ml. of
18 chloroform and 0.5 ml. of phosphorus oxychloride is stirred
19 at reflux for 30 hours. A clear solution is obtained after
20 2-3 hours. After cooling and dilution with chloroform, the
21 mixture is extracted with ice-water. The chloroform layer is
22 separated and evaporated to dryness leaving an oily residue
23 which is triturated with cold dilute hydrochloric acid and
24 filtered. The aqueous extracts are combined, rendered strongly
25 alkaline with 5% aqueous sodium hydroxide, and the oily base
26 extracted into 1:1 benzene:ether. Evaporation of the washed
27 and dried organic extract under reduced pressure leaves a
28 viscous oil containing a mixture of 10,11-dihydro-5-(1-
29 chloro-3-dimethylaminopropyl)-5,10-methano-5H-dibenzo[a,d]
30 cycloheptene and 1-(10,11-dihydro-5,10-methano-5H-dibenzo
31 [a,d]cyclohepten-5-yl)-3-dimethylamino-1-propene. The
32 hydrogen oxalate salt of this product is obtained by treating

1 charcoal catalyst. The product obtained in this manner is
2 similarly separated from the catalyst and recrystallized
3 from a mixture of isopropyl alcohol and water.

4 Various changes and modifications of the invention
5 can be made, and to the extent that such variations incorpo-
6 rate the spirit of this invention, they are intended to be
7 included within the scope of the appended claims.

FLOW SHEET



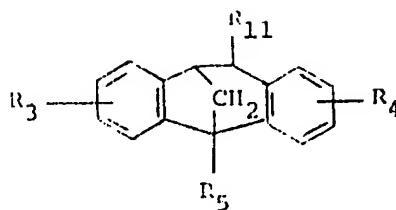
being now particularly described and ascertained my/our said invention and
what manner the same is to be performed, I/we declare that what I/we claim is

1. A compound selected from a 10,11-dihydro-5,10-methano-5H-dibenzo[a,d]cycloheptene having a primary, secondary or tertiary aminoalkyl substituent at the 5-position or a 9-alkanoyl-9,10-ethanodihydroanthracene compound containing an amino, carboxy or esterified carboxy substituent attached to one of the carbons of the ethano bridge.

2. A compound in accordance with Claim 1 comprising a 10,11-dihydro-5,10-methano-5H-dibenzo[a,d]-cycloheptene compound substituted at the 5-position with a primary, secondary or tertiary aminoalkyl substituent.

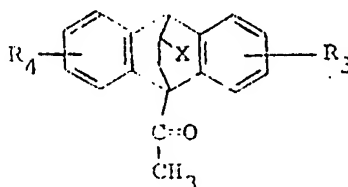
3. A compound in accordance with Claim 1 comprising a 9-alkanoyl-9,10-ethanodihydroanthracene compound wherein one of the carbons of the ethano bridge is substituted with an amino, a carboxy or an esterified carboxy substituent.

4. A compound in accordance with Claim 1 having the structural formula



wherein R_5 is an aliphatic substituent substituted by one or more members selected from the group comprising ketonic oxygen, hydroxyl, amino, alkylamino, or dialkylamino; R_3 and R_4 are hydrogen, halo, alkyl, alkoxy, or trifluoromethyl, and R_{11} is hydroxyl, alkanoyloxy.

5. A compound in accordance with Claim 1 having the structural formula



wherein R_3 and R_4 are hydrogen, halo, alkyl, alkoxy or trifluoromethyl and X is amino, carboxy or esterified carboxy.

6. A compound in accordance with Claim 5 consisting of 9-acetyl-9,10-dihydro-9,10-ethanoanthracene-11-carboxylic acid.

7. A compound in accordance with Claim 5 consisting of 9,10-dihydro-9-(2-methyl-1,3-dioxolan-2-yl)-9,10-ethanoanthracene-11-carboxylic acid.

8. A compound in accordance with Claim 5 consisting of methyl-9,10-dihydro-9-(2-methyl-1,3-dioxolan-2-yl)-9,10-ethanoanthracene-11-carboxylate.

9. A compound in accordance with Claim 5 consisting of methyl-9-acetyl-9,10-dihydro-9,10-ethanoanthracene-11-carboxylate.

10. A compound in accordance with Claim 5 consisting of methyl-9,10-dihydro-9-(2-methyl-1,3-dioxolan-2-yl)-9,10-ethanoanthracene-11-carboxylate.

11. A compound in accordance with Claim 5 consisting of 9,10-dihydro-9-(2-methyl-1,3-dioxolan-2-yl)-9,10-ethanoanthracene-11-carboxylic acid hydrazide.

12. A compound in accordance with Claim 5 consisting of 9,10-dihydro-11-ethoxycarbonylamino-9-(2-methyl-1,3-dioxolan-2-yl)-9,10-ethanoanthracene.

13. A compound in accordance with Claim 5 consisting of 9-acetyl-11-amino-9,10-dihydro-9,10-ethanoanthracene.

14. A compound according to Claim 4 consisting of 11-acetoxy-5-acetyl-10,11-dihydro-5,10-methano-5H-dibenzo[a,d]cycloheptene.

15. A compound according to Claim 4 consisting of 5-acetyl-10,11-dihydro-5,10-methano-5H-dibenzo[a,d]cyclohepten-11-ol.

16. A compound according to Claim 4 consisting of 1-(11-acetoxy-10,11-dihydro-5,10-methano-5H-dibenzo[a,d]cyclohepten-5-yl)-3-dimethylamino-1-propanone hydrochloride.

17. A compound according to Claim 4 consisting of 1-(10,11-dihydro-11-hydroxy-5,10-methano-5H-dibenzo[a,d]cyclohepten-5-yl)-3-dimethylamino-1-propanol.

18. A compound according to Claim 4 consisting of 1-(11-chloro-10,11-dihydro-5,10-methano-5H-dibenzo[a,d]cyclohepten-5-yl)-3-dimethylamino-1-propanol hydrochloride.

19. A compound according to Claim 4 consisting of 1-(10,11-dihydro-5,10-methano-5H-dibenzo[a,d]cyclohepten-5-yl)-3-dimethylamino-1-propanol.

20. A compound according to Claim 4 consisting of 5-acetyl-11-chloro-10,11-dihydro-5,10-methano-5H-dibenzo[a,d]cycloheptene.

21. A compound according to Claim 4 consisting of 5-acetyl-10,11-dihydro-5,10-methano-5H-dibenzo[a,d]cycloheptene.

22. A compound according to Claim 4 consisting of 1-(10,11-dihydro-5,10-methano-5H-dibenzo[a,d]cyclohepten-5-yl)-3-dimethylamino-1-propanone.

23. The process for preparing a 10,11-dihydro-5,10-methano-5H-dibenzo[a,d]cycloheptene compound containing an alkylaminoalkyl substituent attached to the 5-position which comprises heating a 9-alkanoylanthracene in contact with acrylic acid or an ester thereof to form a 9-alkanoyl-9,10-ethano-11-carboxy or carbalkoxydihydroanthracene, subsequently reacting said carboxy or carbalkoxy compound with hydrazine to form the corresponding 9-alkanoyl-9,10-ethanodihydroanthracene-11-carboxylic acid hydrazide, contacting said hydrazide with nitrous acid to form the corresponding 11-urethane and hydrolyzing said urethane to produce 9-alkanoyl-11-amino-9,10-dihydroanthracene, heating said 11-aminoanthracene compound in contact with nitrous acid to form a 5-alkanoyl-10,11-dihydro-5,10-methano-11-hydroxy or acyloxy-5H-dibenzo[a,d]cycloheptene, heating said cycloheptene compound in acid solution in contact with an amine and an aldehyde to form a 5-dialkylaminoalkanoyl-5,10-methano-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, reducing said dialkylaminoalkanoyl cycloheptene compound by heating in contact with an alkali metal borohydride to produce the corresponding 5-(alkylamino-hydroxyalkyl)-5,10-methano-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, dehydrating said hydroxyalkyl cycloheptene compound to form the corresponding 5-alkylaminoalkenyl-5,10-methano-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, and hydrogenating said alkenyl compound in the presence of a catalyst to produce the corresponding 5-alkylaminoalkyl-5,10-methano-10,11-dihydro-5H-dibenzo[a,d]cycloheptene.

5,10-methano-5H-dibenzo[a,d]cycloheptene compound containing an alkylaminoalkyl substituent attached to the 5-position which comprises heating a 9-alkanoylanthracene in contact with acrylic acid or an ester thereof to form a 9-alkanoyl-9,10-ethano-11-carboxy or carbalkoxydihydroanthracene.

25. The process which comprises heating a 9-alkanoyl-9,10-ethano-11-amino-9,10-dihydroanthracene compound in intimate contact with nitrous acid to form a 5-alkanoyl-10,11-dihydro-5,10-methano-11-hydroxy or acyloxy-5H-dibenzo[a,d]cycloheptene.


26. The process which comprises heating a 5-alkanoyl-10,11-dihydro-5,10-methano-11-hydroxy or acyloxy-5H-dibenzo[a,d]cycloheptene in contact with an amine and an aldehyde under acidic conditions to form a 5-dialkylamino-alkanoyl-5,10-methano-10,11-dihydro-5H-dibenzo[a,d]cycloheptene and reducing said dialkylaminoalkanoyl cycloheptene compound by heating in contact with an alkali metal borohydride to produce the corresponding 5,10-methano-10,11-dihydro-5H-dibenzo[a,d]cycloheptene compound having a radical derived from an alkylaminoalcohol attached to the 5-position.

27. Novel derivatives of dibenzocycloheptenes substantially as described herein with particular reference to the accompanying examples.

28. A process for the preparation of dibenzocycloheptenes substantially as described herein with particular reference to the accompanying examples.

29. The product when obtained by the process of any of the claims 23 to 26 and 28.

DATED this 20th day of March, 1968.


PATENT AGENT FOR THE APPLICANTS.